

SURVEILLANCE OF DRUG RESISTANCE IN TUBERCULOSIS IN THE STATE OF TAMILNADU

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Summary: Surveillance of drug resistance was carried out at State level to obtain data which are standardised and comparable using guidelines prescribed by the WHO/IUATLD Working Group on Anti-tuberculosis Drug Resistance Surveillance.

Objective: To determine the proportion of initial and acquired drug resistance in cases of pulmonary tuberculosis in Tamilnadu, in order to use the level of drug resistance as a performance indicator of the National Tuberculosis Programme.

Methods: Two specimens of sputum from each of a total of 713 patients attending 145 participating centres all over the state were tested by smear and culture examination and drug susceptibility tests of Isoniazid, Rifampicin, Ethambutol and Streptomycin.

Results: Out of 400 patients for whom drug susceptibility results were available, 384 (96%) had no history of previous anti-tuberculosis treatment. Of these, 312 (81%) were susceptible to all the drugs tested. Resistance to isoniazid was seen in 15.4% of patients and to Rifampicin in 4.4% including resistance to Isoniazid and Rifampicin in 3.4%.

Conclusion: There has been a gradual increase in initial drug resistance over the years in this part of the country.

Key Words: Pulmonary tuberculosis: Initial drug resistance, Acquired drug resistance.

INTRODUCTION

The level of drug resistance is known to provide an epidemiological indicator to assess the extent of resistant bacterial transmission in the community as well as success or otherwise of the National Tuberculosis Programme (NTP). High levels of resistance have been reported in certain regions of the world, particularly in Asia and parts of Africa^{1,7}. Potential causes of drug resistance include inadequate treatment provided by health services, poor case-holding, poor drug supply, poor quality of drugs, non adherence of patients to the prescribed drug regimens and indiscriminate use of anti-tuberculosis drugs in the private sector. However, the most important cause of drug resistance may be the error the health care workers in not providing correct regimens⁸. High levels of Rifampicin

resistance, for instance, require adjustment of the control programme to guarantee high cure rate.

The recommendation to use drug susceptibility tests for monitoring and guiding tuberculosis treatment programmes was made many years ago⁹. In view of the practical difficulties in collecting comparable data, the World Health Organization (WHO) proposed a programme of global surveillance of drug resistance in tuberculosis through its collaborating centres for bacteriology of tuberculosis which would function as Supranational Reference Laboratories (SRL) for the respective regions⁹. The proposed programme was based on random sampling of patients reporting to clinics for tuberculosis treatment. Susceptibility testing was to be performed by the reference laboratories based on a common protocol including uniform laboratory methods. As a first step, a regional survey was carried out in 10

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Latin American countries¹⁰. The overall experience gained in Latin America suggested that a sample survey of drug resistance with large failure rates of more than 5% may indicate inadequate routine treatment and high levels of initial resistance, which made survey of drug resistance a priority⁸.

Several countries in Asia and Africa undertook national surveys in accordance with the protocol, but regional multi-centre surveys were not completed. Meanwhile, several countries, including Tanzania¹¹ and South Africa¹² established systematic national surveillance programmes. In India, there was an urgent need to establish surveillance of drug resistance at country level to obtain standardized and comparable data within and among countries. In view of the large size of the country, it was proposed to undertake surveillance of drug resistance in one state, Tamil Nadu to begin with, based entirely on the guidelines of the protocol prescribed by the WHO⁸. The study was conducted by the Tuberculosis Research Centre, a WHO collaborating centre.

MATERIAL & METHODS

1. Organizational and Survey Outline

Survey area

The entire State of Tamil Nadu in south India formed the survey area:

Central Laboratory

The Tuberculosis Research Centre (Indian Council of Medical Research), Chennai (TRC) was the National Central Laboratory. All bacteriological investigations namely, smear, culture identification and susceptibility testing were carried out there.

Supranational Reference Laboratory (SRL)

External quality control assessment was carried out at the Centre for Public Health Sciences, Brisbane, Australia which validated the results of susceptibility tests done by the Central Laboratory (TRC). The Brisbane laboratory had already been identified by the WHO as a Supranational Reference Laboratory for the region. The method of quality control, according to internationally accepted standards, was developed by the SRL before starting the survey. Such a system included (a) testing at TRC of a sample of strains sent by the SRL, and (b) re-

testing at SRL of a sample of strains tested at TRC.

Diagnostic Centres

All the District TB Centres (DTC) at the district headquarters and X-ray centres (XC) in taluks of the entire state of Tamil Nadu formed the diagnostic centres. In addition, hospitals attached to the medical colleges in the state were also included. In all, a total of 145 centres participated in the study. They comprised 23 DTCs, 117 XCs and 5 medical college hospitals.

Supervision

A Central Coordinator and a team of medical officers closely supervised all diagnostic centres to ensure good cooperation. They promptly identified and corrected any operational problems. It was also verified that the procedure for sputum smear microscopy followed at the diagnostic centres was of an acceptable standard¹³.

Preparatory Phase

In the preparatory phase of the survey, the Coordinator and the central laboratory jointly assessed all the relevant indicators of the programme, the infrastructure and procedures. Further, the Coordinator arranged a training programme at Chennai for the personnel managing the District Tuberculosis Programmes. During training, the personnel of the Central Laboratory gave a detailed day-long explanation of all aspects of surveillance activities such as case selection, collection of specimens of sputum, entries to be made in the relevant forms and despatch of the specimens to TRC through the postal services. The district personnel, in turn, conducted training programmes for medical officers and laboratory technicians at the XC's of their respective districts.

Data Analysis

The data analysis was done by the TRC using the EpiInfo software.

2. Sampling

It was estimated that a sample size of at least 500 was needed for the overall survey to be able to detect resistance level of about 30% expected in this area with a confidence interval of 26% to 34% and a level of confidence of 95%^{14,15}. Hence, from each of the 145 diagnostic centres.

2 specimens of sputum from 4 to 5 consecutive, newly diagnosed smear-positive cases were collected over a two-month period, about 700 cases in all (allowing for contamination rate of about 5%), and sent to TRC. The diagnostic centres also filled up a form for each specimen giving information about previous treatment the patient had received which was of help in distinguishing between initial and acquired resistance.

3. Intake of patients

Inclusion criteria

Patients were eligible for inclusion if:

1. they had been newly registered (re-registration of the same patient in different centres was to be avoided);
2. they had been found to be sputum-smear positive, at least once during the intake period.
3. Children under 15 years of age fulfilling the above criteria were also eligible.

Transport of sputum specimens

Before the start of the study, the TRC supplied, through the Coordinator, sufficient numbers of sputum collection bottles (sterile universal containers), each containing 5 ml of sterile 1% cetyl pyridinium chloride solution.

At the centres, sputum specimens were collected from patients, smears made, stained by Z-N method and examined as per the programme procedure. If a smear was positive, and the patient fulfilled the other eligibility criteria, two more specimens (5ml each) were collected from the patient in the sputum collection bottles containing CPC.

A total of 1375 sputum specimens was received from 713 patients during February-March 1997. Of these, 51 patients provided only one specimen each while the rest gave two specimens each.

4. Bacteriological investigations at the Central Laboratory

Smear examination

At TRC, smears were made from all specimens, stained by the auramine-phenol method and examined using fluorescence microscopy. Positive smears were graded as 1+, 2+ and 3+¹⁶.

Culture

The specimens were processed by modified petroff's method¹¹⁷, using 4% sodium hydroxide and inoculated on to two slopes of L-J medium. The slopes were incubated at 37° C and examined weekly for evidence of growth till 8 weeks. The growth was graded as 1+ (20-200 cols.), 2+ (more than 100 discrete cols.) and 3+ (confluent growth). Actual colony counts were reported if growth was less than 20 colonies.

Identification

Culture isolates were identified as *M.tuberculosis* based on niacin test, catalase at 68°C/pH 7 and growth on L-J medium with *p*-nitrobenzoic acid^{18,19}

Susceptibility testing

Susceptibility tests were performed for Streptomycin by the resistance ratio (RR) method and for Isoniazid, Rifampicin and Ethambutol using the absolute concentration (MIC) method on L-J medium. A 3mm loopful of suspension of the growth, containing approximately 4 mg/ml, was inoculated on to after 28 days of incubation. Resistance to Streptomycin was defined as RR of 8 or more. An MIC of 1 mg/1 or more for Isoniazid, 128 mg/1 or more for Rifampicin and 8 mg/1 or more for Ethambutol was interpreted as resistant^{20,22}.

RESULTS

Smear

On smear examination at TRC, 6.5% of the 1375 specimens were found to be smear-negative (Table 1). Duplicate smears from the same patient showed a fair agreement with 91% concordance even in grades (Table 2).

Table I. Smear results of all specimens tested

Smear Grade	Total Specimens	
	No.	%
Neg	90	6.5
1 +	1,054	76.7
2+	224	16.3
3+	7	0.5
TOTAL	1,375	100.0

Table 2. Distribution of Smear Results of duplicate specimens from same patient according to grade of smear.

Smear II	Smear I				Total	
	Neg.	1+	2+	3+	No	%
Neg	16	30	3	0	49	6.9
1+	24	425	52	0	501	70.3
2+	1	55	52	1	109	15.3
3+	0	1	0	2	3	0.4
NA	0	42	8	1	51	7.2
Total No.	41	553	115	4	713	
%	5.8	77.6	16.1	0.6		

Culture

A little more than half of all the specimens were culture negative and more than half of all positive cultures yielded 100 colonies or less. An identical pattern was obtained when duplicate specimens from the same patients were examined (not tabulated). The contamination rate was also extremely low (0.6%).

All the strains isolated were identified as *Mycobacterium tuberculosis*.

Drug susceptibility test results were available for 400 patients, including 384 patients without any history of previous treatment and 16 patients with previous treatment. The pattern of resistance observed in these patients is shown in Table 3. Of the 384 patients without any history of previous treatment, the isolates from 312 (81.2%) patients were fully susceptible to all the drugs tested, while isolates from 72 patients had resistance to one or more drugs. Resistance to Isoniazid, alone or in combination with other drugs was seen in 59 (15.4%) patients. Similarly, resistance to Rifampicin, alone or with other drugs was seen in 17 (4.4%) patients. Resistance to Isoniazid and Rifampicin together was observed in 13 (3.4%).

Of the 16 patients with history of previous treatment, isolates from 8 patients were fully susceptible. Resistance to Isoniazid, alone or with other drugs was seen in 8 cases, Rifampicin resistance was observed in 4 patients, all of whom were also resistant to Isoniazid.

External Quality Control Studies

During the study period, two rounds of external

quality assurance studies were undertaken by the Brisbane Laboratory, the results of which are presented in Table 4.

Of the 20 cultures received from the SRL in Round I, there was 100% agreement in the case of Isoniazid and Ethambutol, while it was 95% for Rifampicin and 90% with Streptomycin. However,

Table 3. Summary of anti-tuberculosis drug resistance

	No history of treatment/initial resistance		Previously treated/acquired resistance	
	No	%	No	%
Total tested	384	100.0	16	100.0
Fully sensitive	312	81.2	8	50.0
Any resistance	72	18.8	8	50.0
Resistance to				
H	29	7.6	2	12.5
R	2	0.5	0	0.00
E	2	0.5	0	0.00
S	7	1.8	0	0.00
HR	2	0.5	1	6.2
HRE	4	1.0	2	12.5
HRS	0	0.0	0	0.0
HRSE	71	8	1	6.2
HE	7	1.8	1	6.2
HS	5	1.3	0	0.00
HES	5	1.3	1	6.2
RE	0	0.0	0	0.0
RS	0	0.0	0	0.0
RES	2	0.5	0	0.0
ES	0	0.0	0	0.0
Any H Resistance	59	15.4	8	50.0
Any R Resistance	17	4.4	4	25.0
Any HR Resistance	13	3.4	4	25.0

Table 4. Agreement in drug susceptibility results between TRC, Chennai and SRL, Brisbane*

Retesting at	Reproducibility (%)			
	S	H	R	E
Round I: TRC	90	100	95	100
SRL	100	90	100	100
Round II: TRC	100	100	100	100
SRL	100	100	100	100

*SRL Brisbane used BACTEC radiometric method while TRC used conventional (RR/MIC) methods

Table 5. Comparison of direct culture method with Petroff's method in specimens containing CPC.

Petroff's method	Direct Culture				Total
	Neg.	Col.	1+	2+/3+	
Neg	6	7	3	22	38
Col.	1	0	0	7	8
1+	2	0	0	2	4
2+/3+	0	0	0	4	4
Total	9	7	3	35	54

in Round II, the reproducibility was 100% for all the drugs tested.

Similarly, of the 20 strains re-tested at the SRL in Round I, there was total agreement between the two laboratories in the case of Streptomycin, Rifampicin and Ethambutol. In round II, there was 100% agreement with all the four drugs tested.

DISCUSSION

The WHO / IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance recorded considerable variation in the prevalence of drug resistance among 35 countries in 5 continents. The median prevalence of drug resistance among patients with no history of previous treatment was 10% with the range from 2%-40%¹⁰. Although the prevalence of MDR-TB is generally low, there are several countries where the situation demands immediate intervention. Overall, the median prevalence of primary MDR-TB was 1.4% ranging from 0-14%¹⁰. Among the South East Asian Region (SEAR) countries, the prevalence of primary resistance is readily available only for Nepal and Thailand since they participated in the WHO supported Global Project on Anti-tuberculosis Drug Resistance Surveillance in 1994-1997. The median prevalence of primary resistance to any drug was recorded as 23.2% with range of 9.8% to 36.6%. The median prevalence of primary MDR-TB was 2.5%, significantly higher than the global mean of 1.4%¹⁴. However, such information for other SEAR countries, based on standardized protocols and methods, is not available. Although drug resistant tuberculosis has frequently been encountered in India and its presence has been known from the time drugs were introduced for the treatment of tuberculosis, there is no comprehensive report mainly due to limited facilities

available for culture and susceptibility tests across the country. The present report on drug resistance in the entire state of Tamil Nadu, using internationally acceptable guidelines and a standardized methodology gives reliable information.

Considering smear results of all specimens tested, it was observed that 6.5% of the specimens were negative by microscopy at this Centre. It should be noted that one of the criteria for inclusion of patients in this study was that they should have been smear positive at least once during the study period. The specimens that were sent to TRC were not examined for smear at the diagnostic centres. Hence this discrepancy could have been due to differences between specimens from the same patient. Another explanation could be that the sputum specimens got diluted by the addition of 5 ml of CPC solution which could have resulted in a small proportion of smears being reported as negative. Nevertheless, the agreement of 93.5% shows that sputum microscopy at the diagnostic centres, with minimal infrastructure, was up to an acceptable standard.

That a very large number of smear-positives were culture negative in this study is of utmost concern. This, it was realized, was due to defective methodology provided in the study protocol which laid down that the CPC containing specimens should be processed by Petroff's method using 4% sodium hydroxide (NaOH). This combination of CPC-NaOH was perhaps responsible for culture negativity²³. However, by the time this was realized, the intake was almost completed. However, towards the end of the study, an alternative method of processing was employed. The CPC-containing specimen was directly centrifuged as such and the deposit was inoculated on to two LJ slopes (direct method). Subsequently, the deposit was re-suspended in water to the original volume and processed by Petroff's method. A comparison of the results of this study on 61 specimens is shown in Table 5. It was observed that the direct method yielded 45 positive cultures as against only 16 by Petroff's method, a highly significant difference. Further, 35 out of 54 cultures (64.8%) yielded 2+ /3+ grades as against only 4 (7.4%) by Petroff's method.

The CPC-NaOH combination had not only inhibited the growth of *M. Tuberculosis* but perhaps also that of the contaminants, which accounted for

the very low (0.6%) contamination observed in this study.

This observation has been repeated in a survey conducted by us in North Arcot district (Tamil Nadu), in 1999. A total of 635 sputum specimens from 320 patients were collected in transport medium containing 5 ml of 1% CPC and 2% NaCl solution and were processed directly. An interim analysis has revealed culture positivity of 95%, negativity of 3% and contamination of 2%. The results of this study confirm our earlier observation once again (unpublished data). It might be observed that the 1988-89 level of 2% MDR-TB in the North Arcot district has gone up to about 4% in the succeeding decade.

Considering the level of drug resistance observed in this study, the proportion of resistance to H, R and HR was of the order of 15.4%, 4.4% and 3.4%, respectively, in previously untreated cases. These estimates are similar to other surveys conducted by the TRC in the recent past. Thus, in a study conducted in the North Arcot district of Tamil Nadu during the period 1985-89 on 2,779 cases, with no history of previous anti-tuberculosis treatment or with previous treatment of less than 2 months' duration, initial resistance to H was 13% and HR resistance was 1.6%¹⁴. In the district of Raichur in Karnataka State, initial resistance to H was of the order of 13.2%²⁴. Data from TRC on primary resistance among 6,742 patients, from 1956 onwards for 18 different chemotherapeutics, had shown a gradual increase in the prevalence of primary resistance to anti-tuberculosis drugs. For Isoniazid and Streptomycin, the resistance rates were similar and ranged from 3-14% with the highest level of 14% observed during 1990 for Isoniazid. Initial resistance to Rifampicin started appearing during the 1990s and is 1.2% at present. Resistance to HR or SHR was observed to be less than 1% in 1990-95⁷. However, observations on acquired resistance in India vary in different surveys. A retrospective analysis on a cohort of 3,357 smear-positive patients initiated on anti-tuberculosis treatment, between April 1986 and March 1988 in North Arcot District had shown acquired resistance of 67% to H and 12% for R, either alone or in combination with other anti-tuberculosis drugs²⁵.

Elsewhere in India, an alarmingly high proportion of acquired resistance has been reported

from the state of Gujarat²⁶, resistance to H being 35-60% and 3-37% for R. Other recent reports on acquired resistance (from previously treated cases) in centres such as Sewagram, Wardha (1982-89), New Delhi (1990-91) and Tamil Nadu (1995) showed a high level of resistance to Isoniazid (20.9%, 50.7% and 23.6% respectively) and MDR-TB (9.6%, 33.7% and 23.3% respectively)²⁷⁻²⁸ are not surprising considering their specialized status where chronically ill patients with a history of mismanagement and bad treatment are referred. On the other hand, drug resistance reported from the Military Hospital at Pune showed a very low level of initial resistance to H (0.6%) which could be due to the minimal chance of indiscriminate treatment received prior to reporting at the hospital³⁰.

There has perhaps been a gradual increase in primary drug resistance in this part of India, over the years. However, there appears to be a marginally higher acquired resistance, which contributes to the problem of rise in primary drug resistance. This could be overcome by a strong control programme which can reduce the creation of drug resistance in the community such as directly observed therapy with short course regimens (DOTS)⁴. Since no newer drugs for tuberculosis are likely to become available in the near future, the only options left for the prevention of drug resistance are effective case-finding, prompt and correct diagnosis and successful treatment of patients. Apart from a strong control programme, continuous surveillance of drug resistance will provide information which will serve as a useful parameter in the evaluation of control programmes.

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Smoking Withdrawal Syndrome

Inhaled nicotine bonds with some receptors in the body which provide perceived pleasurable feelings. When the effect of nicotine dissipates, the receptors send signals to the brain which are perceived as a displeasurable feeling - the withdrawal syndrome - compelling the smoker to light up.

The act of smoking does not, however, happen in a vacuum: It is almost always attended with particular “settings”, situations or emotions peculiar to each individual’s desires. These unfulfilled desires make the withdrawal symptoms all the more painful. It is mainly the psychological associations which urge a smoker to resume smoking. Or when the nicotine level in the body is low enough to trigger the receptors. Smokers associate cigarettes and smoking with many aspects of their daily life. Whenever these associations recur, there is a craving to smoke.

After stopping smoking, the physical effects of the withdrawal persist for between 7 to 30 days. However, the craving for a cigarette continues for months, despite the withering away of receptors after having been deprived of nicotine. The craving persists because of the associated settings and human emotions of the smoker.

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